MINIREVIEW

The G Protein Subunit Gene Families

G. B. Downes*,[1] and N. Gautam*,†,[2]

*Department of Anesthesiology and †Department of Genetics, Washington University School of Medicine, St. Louis, Missouri 63110

Receptors on cell membranes sense a variety of signals such as neurotransmitters, hormones, and light. The vast majority of such receptors are coupled to G proteins, which transduce the signal to effectors. G proteins are heterotrimers made up of an α, a β, and a γ subunit (29). The G protein subunits are now known to be encoded by families of related genes in mammalian cells (74). The sizes of these mammalian gene families vary. α subunits are encoded by 16 genes, β subunits are encoded by 5 genes, and γ subunits are encoded by 12 genes.

After the initial discovery of G proteins, most work focused on the α subunit. To identify the molecular basis for diversity in α subunit types, genes for this subunit were cloned and characterized (41). Additional interest in the α subunit genes was stimulated by the discovery of mutations in these genes associated with human disease (76). In the past few years, several genes for the β and γ subunits have also been identified and characterized (18, 19, 22, 38, 64, 73, 80). Information about these three gene families has also come from the large-scale human and mouse genome sequencing efforts. The recently completed characterization of the genomes of *Saccharomyces cerevisiae* and *Caenorhabditis elegans* allows us to compare the size and extent of diversity of the mammalian G protein subunit gene families with that of a unicellular eukaryote and a lower invertebrate (http://www.ncbi.nlm.nih.gov/PMGifs/Genomes/yc.html and http://www.ncbi.nlm.nih.gov/PMGifs/Genomes/ce.html). We focus here on some aspects of the G protein subunit genes: (i) We summarize the existent information on the structure, expression, and organization of these genes. (ii) We focus on mutations in the genes for G protein subunits that result in disease and the molecular basis for their deleterious effect on cells. (iii) We discuss the implications of the increase in diversity and size of the G protein subunit gene subfamilies with cellular complexity. Recent reviews focusing on various related aspects of G proteins are available (21, 27, 32, 62).

G Protein Subunit Function

The α subunit is a GTPase. When the receptor stimulates the G protein, the α subunit releases GDP and binds GTP. In this activated state, several α subunit types act directly on effector molecules to modulate their activity. α subunit types range in size from 39 to 52 kDa (29). Some α subunits show specificity for effectors—αs activates adenylate cyclases, αi inhibits adenylate cyclases, and αq activates phospholipase C isozymes (32). Specificity of α subunit types for receptors has also been demonstrated in a few cases (15, 31). Comparison of the amino acid sequences of 16 known mammalian α subunit types indicates that they fall into four subfamilies (74) (Table 1).

The β subunit is tightly bound to the γ subunit and is known to function only as such a complex. The $\beta\gamma$ complex modulates the activity of several effectors. The β subunit binds a variety of effectors and is therefore directly involved in the modulation of effector activity (9, 14). The five β subtypes identified so far are all approximately 36 kDa in size. They essentially fall into two subfamilies based on amino acid homology (86) (Table 2). Consistent with this grouping, β5 has been shown to have distinct properties in comparison to β1–β4 (50, 95).

Each of the 11 mammalian γ subunit types is approximately 7–8 kDa in size. The 12 C-terminal residues of one of the γ subunit types, γ1, has been shown to interact with a receptor (43, 44). Based on homology in this C-terminal domain and overall homology, the γ subunits have been grouped into four subfamilies (27) (Table 3). The implication from this grouping is that γ subunits that share identical C-terminal sequences interact with the same receptor while γ subunits with different C-terminal sequences interact with distinct receptors.

When the amino acid sequences of members of the α, β, and γ subunits are compared across mammalian species (http://www.ncbi.nlm.nih.gov/Entrez/), they show conservation approaching complete identity. This conservation of primary structure over extended periods of evolutionary history suggests that the differences among the G protein subunit types are of functional significance. The mouse α15 subunit type is a surprising exception to this generally high level of conservation, sharing less than 90% identity with its human homologue (89).

G Protein Subunit Gene Structure

Several of the genes for the α subunits have been characterized. Genes for αi1, αi2, αi3, αt1, α11, and α15 have intron–exon structures that are conserved (17, 34, 67). All of these genes possess eight exons that encode the protein product (Fig. 1A). There is no evidence for alternatively spliced products being encoded by these genes. The conservation of gene structure among the genes encoding the αq and αi subfamilies is consistent with the closer relationship between the α subunits in these two groups at the amino acid level (Table 1). The αo gene, which falls within the αi subfamily,

[1] Present address: Department of Cell and Developmental Biology, University of Pennsylvania, Philadelphia, PA 19104.

[2] To whom correspondence should be addressed at Box 8054, Washington University School of Medicine, St. Louis, MO 63110. Telephone: (314) 362-8568. Fax: (314) 362-8571. E-mail: gautam@morpheus.wustl.edu.

Genomics 62, 544–552 (1999)
Article ID geno.1999.5992
0888-7543/99 $30.00

TABLE 1

Identity Matrix of Mammalian G Protein α Subunits

Subfamily		αolf	αi1	αi2	αi3	αoa	αt1	αt2	αgus	αz	αq	α11	α14	α15	α12	α13
αs	αs	**77**	40	40	40	42	39	40	41	37	39	40	39	35	36	36
	αolf		41	41	40	42	42	42	42	38	39	39	38	35	36	37
αi	αi1			**87**	**93**	**72**	**67**	**69**	**67**	**67**	50	51	51	43	42	39
	αi2				**85**	**68**	**65**	**69**	**66**	**66**	50	50	50	43	41	40
	αi3					**66**	**61**	**65**	**62**	**65**	50	48	48	41	39	36
	αoa						**61**	**61**	**61**	**59**	50	49	50	41	43	42
	αt1							**78**	**75**	**53**	52	51	48	44	41	38
	αt2								**79**	**57**	51	50	49	43	41	38
	αgust									**57**	51	50	50	41	41	40
	αz										49	48	48	41	41	39
αq	αq											**84**	**76**	**54**	41	43
	α11												**82**	**56**	43	44
	α14													**54**	42	44
	α15														40	38
α12	α12															**67**

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST (NCBI). Boldface numbers indicate sequence comparisons between α subunits of the same subfamily. Grouping into subfamilies is based on Simon *et al.* (74). The following sequences have been used for comparison with their GenBank accession numbers given in parentheses: human αs (386743), human αolf (4097329), human αi1 (121019), human αi2 (121023), human αi3 (120996), mouse αoA (120975), human αt1 (121032), human αt2 (232151), rat αgust (121036), human αz (121005), human αq (2506475), human α11 (3041682), human α12 (417030), human α13 (2494886), mouse α14 (232137), and mouse α15 (232138).

has a structure that is similar to the genes in the αi/αq subfamily. However, it contains two additional exons (7A and 8A) downstream of exons 7B and 8B (81) (Fig. 1B). There is a high level of homology between the corresponding pairs of exons—7A/7B and 8A/8B. Alternatively spliced cDNAs containing either of these two pairs of exons are expressed from this gene (78). These splice products encode the αoA and αoB proteins. Since the C-terminal portion of the α subunit has been implicated in receptor interaction (32), evidence for splicing at the C terminus raised the possibility that these two α subunits, αoA and αoB, couple selectively to different receptors. Consistent with this notion, antisense DNA specific to these α subunit types, when injected into GH3 cells, selectively inhibited signaling from the muscarinic or somatostatin receptors (45). In contrast to members of the αi and αq subfamilies, the αs gene is split into 14 protein encoding exons. Several different splice products originate from this gene (42, 46) (Fig. 1B). However, this alternative splicing occurs within the first 5 exons. Variants containing different C-terminal tails with the potential to couple to different receptors are not therefore generated. Significant differences in the properties of the αs splice products have not been shown.

The genes for the β subunits have not been as well characterized as the α subunits. The β3 gene is made up of at least 11 exons (73; and GenBank Accession No. 1633547). The protein-encoding region spans nine exons (Fig. 1C). Analyzing the sequence information for the β2 gene in the GenBank database (AF053356) indicates that the protein-encoding region of the β2 gene is similarly spread over nine exons. The exon–intron structures of the two genes are strikingly conserved with reference to the encoded proteins. Comparison of the β2 and β3 genes with sequence data for a partially characterized β1 gene (AL031282) indicates that the gene structure of the entire family may be completely conserved. Splice variants of the β1–β4 subfamily have not been detected. In contrast, a splice variant of the β5 cDNA containing additional 5′ nucleic acid sequence compared to the β5 cDNA has been identified (85). This results in a β5 product with an additional 42-amino-acid sequence at the N terminus (β5L). The relationship between these cDNAs and the gene structure is unclear since the β5 gene has not been characterized so far.

The G protein β subunits are folded into a propeller-like structure (75, 84). Each blade of this propeller is made up of a β sheet of four β strands. There is no clear correspondence between the positions of the β sheets or a recurrent Trp-Asp motif (WD repeat) and exons in the β subunit genes (Fig. 1C). There is also no clear correspondence between domains on the β subunit that are involved in interaction with effectors (9, 25, 92) and gene structure.

Several of the G protein γ subunit genes have been characterized (18, 22, 38, 64, 80; and GenBank Accession Nos. AC002076 and AC005512). The genes are split into three exons, except for the human gene for γ5, which consists of

TABLE 2

Identity Matrix of Mammalian G Protein β Subunits

	β2	β3	β4	β5
β1	87	80	86	51
β2		81	88	52
β3			78	52
β4				53

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST P (NCBI). Grouping into subfamilies is based on homology. The following sequences have been used for comparison, with GenBank accession numbers given in parentheses: human β1 (121008), human β2 (121010), human β3 (121011), mouse β4 (121012), and human β5 (3023845).

TABLE 3

Identity Matrix of Mammalian G Protein γ Subunits

	γc	γ11	γ2	γ3	γ4	γ5	γ8	γ10	7γ	γ12
γ1	64	75	41	40	35	31	38	38	41	46
γc		65	48	44	40	32	33	39	48	48
γ11			42	42	40	33	40	36	44	48
γ2				79	76	48	71	55	75	65
γ3					68	46	57	50	63	61
γ4						44	63	47	62	58
γ5							46	52	51	44
γ8								59	59	53
γ10									52	48
γ7										77

Note. Numbers indicate the percentage amino acid identity between subtypes calculated using the default settings of BLAST (NCBI). Grouping into subfamilies is based on the C-terminal sequences as well as overall homology (27). The following sequences have been used for comparison; their GenBank accession numbers are indicated in parentheses: human γ1 (585181), human γc (3023844), human γ11 (995921), bovine γ2 (121016), mouse γ3 (3983451), mouse γ4 (1730220), human γ5 (3851089), human γ7 (4826746), rat γ8 (1169865), human γ10 (995919), and bovine γ12 (2494918). γ13 (AI454466 & H46116) has been recently reported (note in proof).

four exons (55). An intron splits the coding region in all γ subunit genes. The position of this intron is conserved with reference to the amino acid sequence among homologous and orthologous γ subunit genes (18). As in the case of the α subunit and β subunit genes, there is no clear correspondence of secondary structure domains with exons in the γ subunit genes (Fig. 1D).

Although the gene products in Tables 1, 2, and 3 are from different mammalian species, there is evidence from the database that all 16 α subunits, 11 γ subunits, and the β subunits other than β4 are expressed in at least two different mammals (β4 cDNA has been isolated only from mouse). It is therefore highly likely that the genes for each of the G protein subunit gene families are conserved in all mammals.

Organization of the G Protein Subunit Genes in Mammalian Genomes

Efforts from individual laboratories combined with large-scale EST mapping programs have resulted in the identification of most G protein subunit gene loci in the mouse and/or human genomes (Table 4). Notably, four pairs of the α subunit genes—*Gnai3/Gnat2; Gnat1/Gnai2; Gna15/Gna11;* and *Gnaq/Gna14*—have been found to be arranged as tandem duos in both the mouse and the human genomes (70, 89). The genes constituting two of these gene duos, *Gna11/Gna15* (mouse) and *GNAQ/GNA14* (human), lie in a head-to-tail arrangement (17, 70). The functional significance of this tandem organization is unclear. However, the mapping data have been used to provide a model of α subunit gene evolution (89). According to this model, genes in the αi and αq class descended from a common or independent progenitor(s) that had undergone tandem duplication. The genes for αz (*Gnaz*), αi-1 (*Gnai1*), and αoa (*Gnao*), however, do not seem to possess a tandem partner. It is hypothesized that a linked gene was lost entirely or partially (in the case of *Gnao*, which expresses products that are spliced). Alternatively, some of these genes may have evolved before the duplication event. The fewer number of exons in the αz gene in comparison to the gene encoding the αi3 subunit (Fig. 1A) does indicate that it diverged from the αi3 gene earlier in evolution than the genes for the αi1, αi2, αo, αt1, and αt2 subunits.

Most of the β and γ subunit genes have also been mapped (1, 19, 30, 38, 64, 72, 87) (Table 4). These genes are well dispersed in both the mouse and the human genomes with the exception of a tandem pair of γ subunit genes—the *GNGT1* (γ1) and *GNG11* (γ11) genes (AC002076). They are in a head-to-tail orientation separated by a distance of >10 kb. In addition, the mouse γ3 gene is organized in a head-to-head fashion with a linked gene, *Gng3lg*, of unknown function (18). This organization is conserved in the human genome (G.B.D. and N.G., unpublished results). The orientation, the close proximity of transcription initiation sites, and the expression patterns of these two genes raise the distinct possibility that shared regulatory elements are used to control their expression.

Comparison of the organization of the mammalian G protein subunit genes with their organization in *C. elegans* does not provide clear insights into the genesis of their diversity. In *C. elegans* the α subunit genes are distributed over several chromosomes with some clustering on two—chromosomes I and V (35). While one of these clusters contains a homolog of the mammalian αi subfamily, the other does not contain any such mammalian homologue.

Subunit Expression

In terms of tissue-specific expression, mammalian G protein subunit genes fall into three categories (Table 5): (i) G protein subunit genes that are expressed ubiquitously or in many tissues; (ii) a subset of genes that is expressed mainly in one tissue—β5, γ3, and γ4 in the nervous system and α15 in hematopoietic cells; and (iii) a smaller subset that is expressed in a specialized cell type—genes for αt1/γ1 in rod photoreceptors, genes for αt2/γc in cone photoreceptors, and the gene for αgust in taste buds. The reasons for specific expression of some G protein subunit genes in a particular tissue are unclear. Restricted expression of the genes for αt1/γ1 in rod photoreceptors is more likely due to the particular requirements of signal amplification in the rhodopsin–Gt system rather than for achieving specificity since it has been shown that Gt1 interacts more effectively with rhodopsin than Gi or Gs (12, 43).

Recent examination of αs expression in mice indicates that even though a G protein subunit may be expressed widely in mammalian organs, it may show subtle variations in expression between tissues. Studies on *Gnas1* gene knockout mice

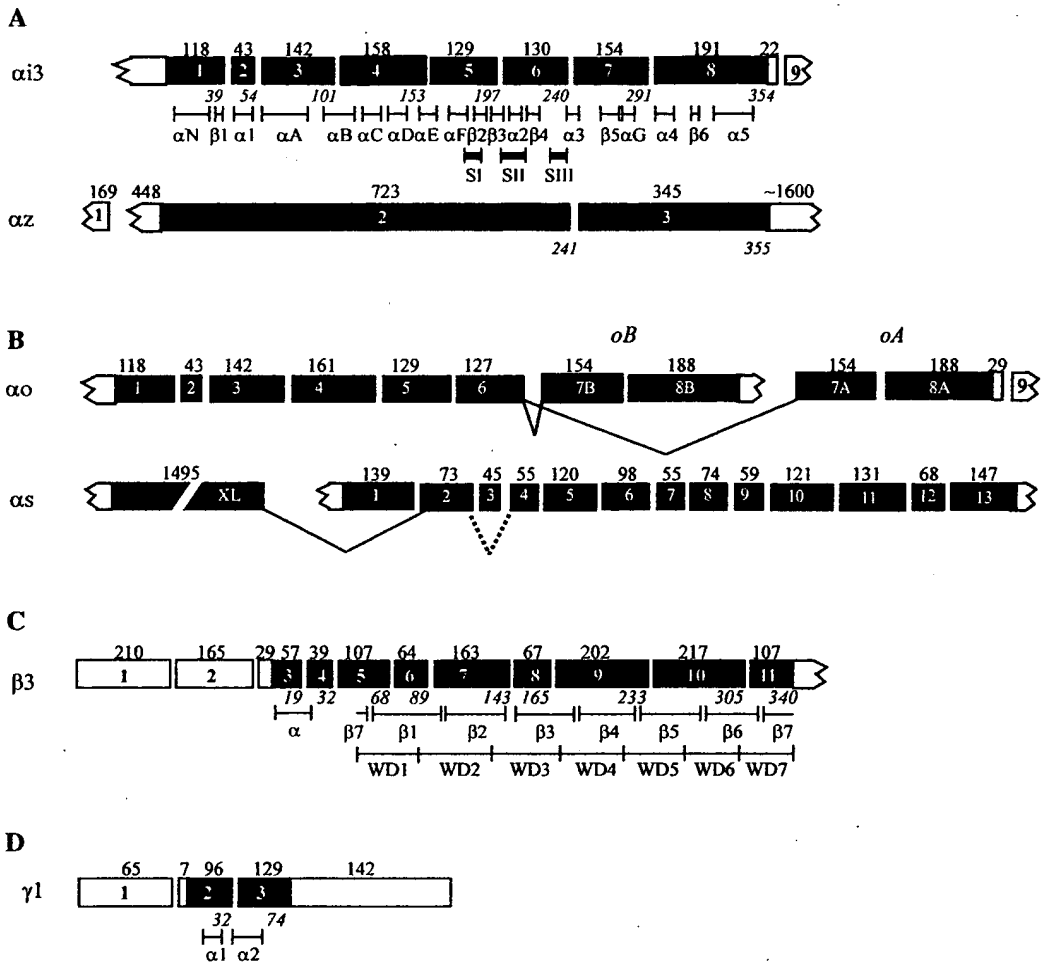

FIG. 1. Structure of G protein subunit genes. **(A)** Structure of the human genes for αi3 (34) (AH001471) and αz (56) (see rat αz, U77483, U77484, and U77485). Since the α subunit types most likely have a conserved tertiary structure, the secondary structure domains from the crystallized αt protein (47) are aligned below. SI, SII, and SIII are switch regions that undergo conformational changes during nucleotide exchange. **(B)** Structure and potential splice products from the human αo (81) (AH002708) and αs (46) (AH002748) genes. The αo gene yields two splice products—αoA and αoB. There are at least five αs splice products: (i) containing the XL exon instead of exon 1 (42) (ii) exon 3 spliced out with two different splice junctions; and (iii) exon 3 retained with two different splice junctions. The αz gene is in alignment with the αi3 gene (intron between exons 6 and 7 of *GNAI3* is conserved as the intron between exons 2 and 3 of *GNAZ*). **(C)** Structure of the human β3 gene (1633547). **(D)** Structure of the bovine γ1 gene (80) (S62029 and S62031). The secondary structure elements of the β1 subunit and γ1 subunit from the crystal structure of the complex (75) are shown at the bottom. The positions of WD repeats are from the primary structure of β2 (23). Boxes indicate exons. Length in basepairs is shown above the boxes, and length in amino acids is shown below the boxes. Filled boxes indicate protein encoding regions. Jagged edges indicate either that the entire exon is not shown or that the exon is not fully characterized. Alternative splicing is indicated by solid or dashed lines.

indicate that this gene is paternally imprinted in a tissue-specific manner (94). The implications of this finding are discussed in the next section. Analysis of the locus in mice that contains the *Gnas1* gene indicates that three genes are clustered in this region—*Gnas1, Gnasxl,* and *Nesp* (66). Notably, they are part of a single transcription unit. The products of the *Gnasxl* and *Nesp* genes are spliced onto exon 2 of *Gnas1*. *Gnasxl* is maternally imprinted, and *Nesp* is paternally imprinted. These two genes show patterns of methylation consistent with this imprinting. However, *Gnas1* is not methylated, and it is hypothesized that in tissues where *Gnaxl* is maternally imprinted the expressed paternal allele competes for transcription factors with the paternal allele of *Gnas1* and silences it.

Diseases Associated with Defects in G Protein Subunits

The alterations in G protein α subunits that lead to human disease can be (i) modifications introduced by extraneous agents, (ii) somatic mutations, and (iii) heritable mutations (Table 4).

(i) Cholera toxin and pertussis toxin are two toxins that ADP ribosylate certain G protein α subunits and profoundly alter their function. Cholera toxin from *Vibrio cholerae* is an ADP ribosyltransferase that transfers the ADP group from NAD to αs (59). The target residue is Arg 201 in αs. This residue is involved in stabilizing the transition state during the hydrolysis of GTP to GDP. The presence of a bulky ADP ribose group at this position thus prevents GTP hydrolysis. The resultant constitutive function leads to high cAMP levels and extrusion of chloride ions and water from intestinal cells. Pertussis toxin from *Bordetella pertussis* ADP ribosylates a Cys residue at the C terminus of several G protein α subunits (59). Since the C terminus is involved in interaction with the receptor, the attachment of an ADP ribose moiety prevents receptor

TABLE 4

The Mammalian G Protein Subunit Genes

Gene symbol	Encoded proteins	Human genome location	Potential disease association
GNAS1	αs-S-A, αs-S-B, αs-L-A, αs-L-B, αs-XL	20p13 (Hs. 113368)[a] (79)	Pseudohypoparathyroidism, McCune–Albright syndrome (76)
GNAL	αolf	18p (Hs. 154145) (89)	
GNAI1	αi1	7q21 (Hs. 203862) (89)	
GNAI2	αi2	3p21[b] (Hs. 77269) (89)	Ovarian and adrenocortical tumors (21)
GNAI3	αi3	1p13[b] (Hs. 73799) (89)	
GNAO	αoA, αoB	16 (89)	
GNAT1	αt1	3p21[b] (Hs. 51147) (89)	Nougaret form of congenital stationary night blindness (20)
GNAT2	αt2	1p13[b] (Hs. 36973) (89)	
GNAG	αgust	ND[c]	
GNAZ	αz	22q11 (Hs. 92002) (89)	
GNAQ	αq	9q21 (Hs. 180950)	
GNA11	α11	19p13[b] (Hs. 1686) (89)	
GNA12	α12	7p[d] (Hs. 73797) (89)	
GNA13	α13	17q22–q24[d] (Hs. 1666) (89)	
GNA14	α14	9q21[b] (70)	
GNA15	α15	19p13[b] (Hs. 73797) (89)	
GNB1	β1	1p36 (Hs. 215595)	
GNB2	β2	7q22 (Hs. 91299) (30)	
GNB3	β3	12p13 (Hs. 71642)	Hypertension (73)
GNB4	β4	ND	
GNB5	β5, β5L	15 (Hs. 155090)	
GNGT1	γ1	7q21.3, 7q31–32[b,e] (Hs. 73112) (72)	
GNGT2	γCone	17q21 (64)	
GNG11	γ11	7q31–32[b] (Hs. 83381)	
GNG2	γ2	10q[d] (19)	
GNG3	γ3	11 (Hs. 179915)	
GNG4	γ4	1 (Hs. 32976)	
GNG5	γ5	1p22 (Hs. 5322) (1)	
GNG7	γ7	19p or 12q[d] (Hs. 127828) (87)	
GNG8	γ8	19q[d] (19)	
GNG10	γ10	9q[d], 9, and 15[f] (Hs. 79126) (19)	
GNG12	γ12	2p[d] (19)	

[a] Unigene (http://www.ncbi.nlm.nih.gov/UniGene/) database accession number.
[b] Indicates colocalization with another G protein subunit gene.
[c] Locus not determined.
[d] Loci predicted based upon mouse mapping data.
[e] There is a discrepancy between the data in the publication and those from the database.
[f] Two loci have been identified.

activation of the G protein. Both cholera and pertussis toxins have been used widely in experiments to perturb signaling mediated by susceptible G proteins or to label α subunits with a radioactive ADP ribose.

(ii) Not surprisingly, mutations that alter Arg201 in αs lead to disease. Some adenomas of the thyroid and pituitary glands contain substitutions at this position of αs (21). The mutant αs is incapable of hydrolyzing GTP and is constitutively active. This constitutive activity is presumably at the basis of the hyperproliferation. McCune–Albright syndrome is characterized by a variety of abnormalities and is associated with mutations at the same position on αs (88). These mutations are, however, somatic. Their effects depend on (a) when they arise during development—late in the case of adenomas and early in the case of McCune–Albright syndrome and (b) where they occur—the effect of the mutant is dependent on the signaling pathways active in the cell type where it is expressed.

(iii) Pseudohypoparathyroidism Type I is a disease that results from a defective αs (11, 51). It is the best characterized and most convincing example of a heritable disorder resulting from mutations in the gene for a G protein subunit. Affected individuals are heterozygous for αs mutations and have shortened fingers, toes, and stature (Albright hereditary osteodystrophy (AHO)). Some do not respond to parathyroid hormone while retaining response to other hormones such as vasopressin. This variation in the phenotype of individuals despite genotypic equivalence was a puzzle for many years. Extensive analysis of the pattern of inheritance of these phenotypes indicated that the αs gene was paternally imprinted (16). The analysis of mice with their αs gene knocked out provided elegant support for this notion and also showed that the imprinting of the αs gene was conserved across mammalian species (94). Knockout mice that were heterozygous for the defective allele of *Gnas* showed the more extreme disease phenotype—resistance to parathyroid hormone—when the mutant allele was inherited from the mother. Furthermore, the differential imprinting was observed between tissues in the kidney. This may explain the variation in response to hormones among heterozygous individuals.

Considering the central role that the G protein βγ complex plays in signaling, it would be expected that mutations in the

TABLE 5

Tissue Distribution of α, β, and γ Subunits

	Tissue distribution
αs	Ubiquitous[a] (8, 48)
αolf	Olfactory neuroepithelium, low levels in brain (5, 37)
αi1	Several (8, 37)
αi2	Several (8, 37)
αi3	Several (37, 48)
αo	Predominantly expressed in brain, other tissues (3, 8, 37)
αt1	Retinal rod cells (49)
αt2	Retinal cone cells (49)
αgust	Taste buds (57)
αz	Predominantly expressed in brain, other tissues (24)
αq	Ubiquitous (90)
α11	Several (90)
α12	Ubiquitous (77)
α13	Ubiquitous (77)
α14	Several (90)
α15	Tissues of hematopoetic lineage (90)
β1	Ubiquitous (6, 23, 48, 53)
β2	Several (6, 23, 53)
β3	Several (6, 52, 53)
β4	Several (6, 53, 83)
β5	Brain (6, 53, 86)
γ1	Retinal rod cells (65)
γc	Retinal cone cells (64)
γ11	Several, undetectable in brain (68)
γ2	Predominantly expressed in brain, other tissues (2, 6, 26)
γ3	Abundant in brain, low levels in testis (28)
γ4	Brain, other tissues[b] (6, 39, 68)
γ5	Ubiquitous (2, 6, 18)
γ7	Predominantly expressed in brain (striatum), other tissues (6, 10, 87)
γ8	Olfactory neuroepithelium, lower levels in brain (6, 71)
γ10	Ubiquitous (6, 68)
γ12	Ubiquitous (6, 58)

[a] For the purposes of this table, "ubiquitous" is defined as being present in all samples, with at least 10 tissues examined.

[b] There is a discrepancy between the data presented in these papers.

β and γ subunit genes too will lead to disease. So far, evidence for such mutations is limited. A mutation in the β3 subunit gene has been shown to be associated with hypertension (73). Other evidence, however, has indicated a lack of association between the mutation in the β3 gene and disease (7, 40). It is possible that many mutations in G protein subunits prove to be lethal because of their central role in mammalian physiology. As a result of the characterization of mammalian genomes, wider searches for mutant genes are now possible. It is likely that such searches will yield additional mutations in the genes for G protein subunits that are at the basis of disease.

One of the aims of gene mapping is to identify linkage to disease loci. The map positions of several G protein subunit genes in mice lie close to mutations that have deleterious effects on the animals (Mouse Genome Database, The Jackson Laboratory; http://www.informatics.jax.org/). It is unclear, however, whether these mutations lie within one of the G protein subunit genes.

Subunit Diversity

At least 20 α subunits are expressed in mammalian cells when splice variants are included. As mentioned before, they can be grouped into four subfamilies as in Table 1. For the most part, the relationships among members in a subfamily are not functional and are likely evolutionary. For instance, αt1 activates cGMP phosphodiesterase, αo modulates the Ca^{2+} channel function, and the αi subtypes inhibit adenylyl cyclase although they all fall within the same subfamily (60). Each subfamily of α subtypes has more than one member (Table 1). The reasons for this pattern of diversity can be inferred from the nature of G protein α subunit diversity in lower eukaryotes—the unicellular yeast *S. cerevisiae* and the multicellular nematode *C. elegans*. The genomes of both these organisms have been sequenced. The yeast genome contains the genes for two α subunit types (M15867 and U18778). These yeast α subunits are most related to the αi subfamily in mammals. *C. elegans* has 20 α subunit genes and 4 gene products, which are homologous to one each of the mammalian subfamilies—αs, αi, αq, and α12 (35). The remaining 16 *C. elegans* α subunit genes cannot be grouped with any of the mammalian α subunit gene subfamilies. Most of these 16 genes are expressed in chemosensory neurons (35). It is most likely that *C. elegans* α subunits that are not homologous to mammalian α subunits are involved in chemosensation or in the development of chemosensory neurons. The presence in *C. elegans* of only a single member belonging to each of the four mammalian subunit subfamilies contrasts with the existence of several members of each α subunit subfamily in mammals. The expansion of a few distinct α subunit genes into subfamilies is most likely specific to organisms that possess a variety of cell types organized into organs of specialized function. Expansion in the case of *C. elegans* is restricted to the α subunits involved in chemosensation. A possible reason for the expansion of subfamilies in mammals is that various cell types and organs with specific functions require distinct signal transduction pathways. The pattern of diversity seen in the case of the genes for the G protein β and γ subunits and receptors further supports the notion that the expansion of subfamilies in signal transducing proteins is correlated with increasing complexity of cellular organization.

While mammals have five β subunit genes that fall into two classes, β1–β4 and β5, yeast has one β subunit gene, STE4 (M23982). The yeast β subunit shows the same level of relatedness to the mammalian β1 and β5 subfamilies. *C. elegans* has two β subunit genes that fall separately into the β1 and β5 mammalian classes (http://www.sanger.ac.uk/Projects/C_elegans). The genes for the 11 γ subunit types in mammalian cells fall into three or four subfamilies (27) (Table 3). Yeast has one γ subunit gene, STE18 (M23983), whose product shows a very low level of homology to mammalian γ subunits. The two γ subunit genes in *C. elegans* do not easily fall within the mammalian subfamilies (http://www.sanger.ac.uk/Projects/C_elegans).

The increase in size of subfamilies of G protein subunit genes in mammals compared to yeast or *C. elegans* is also seen among the genes for receptors. Mammalian genomes contain families of genes encoding receptors that sense the same neurotransmitter or hormone. For example, there are 5 muscarinic acetylcholine receptors, 5 dopamine receptors, at least 13 5-HT receptors, and 3 each of the α1, α2, and β adrenergic receptors (http://www.gcrdb.uthscsa.edu). In contrast, a similar level of diversity within subfamilies of genes for neurotransmitters or peptide receptors is not seen in the *C. elegans* genome (4). One prediction is that when the functions of *C. elegans* receptors are identified, families of sub-

types will be virtually absent. The presence in mammals of subfamilies of genes for receptors is consistent with the existence of subfamilies of genes for G protein subunit types. G proteins containing different subunit types may discriminate between subtypes of receptors that detect the same signal.

It is notable that the mammalian G protein α and γ subunit genes are much more diverse than the β subunit genes (Tables 1 and 3 compared to Table 2). This may be a reflection of the extent of functional diversity at the level of the encoded proteins. Both the α and the γ subunits have been shown to contact receptors specifically (15, 33, 43, 44, 69). Since the seven transmembrane receptor family is large and extremely diverse, variety in G protein α and γ subunit types may allow for specificity in receptor–G protein coupling. Diversity in α subunit types also contributes toward specificity for effectors. For example, αq activates phospholipase C-β and αs activates adenylyl cyclases (32). Although the β subunits have also been shown to interact with effectors, evidence for specificity between β subunit types and effectors is limited (13, 25, 54, 92, 93). Thus one explanation for the presence of more diverse α and γ subunits compared to the β subunits is diversity of function. The effect of knocking out certain α subunit types in mice does support this notion. Mice carrying null alleles of the αo, α13, and αq genes show distinctive phenotypes (36, 61, 63, 82). However, the effect of knocking out other G protein α subunits in mice does not entirely support a simple relationship between gene diversity and functional specialization. Knockouts of the αi1, αi3, α11, α14, and α15 genes, for instance, do not show any obvious defects (62). Although it is still possible that subtle defects in these mice are yet to be identified, these results are consistent with earlier indications from reconstitution experiments that some G protein α subunit types are capable of interacting with diverse receptors (31). Analysis of particular signaling pathways in mutant mice also supports a certain level of redundancy. For instance, Ca^{2+} release, which is mediated by members of the αq subfamily, was not affected in cells that were mutant for αq, α11, or α14, although these were the three members of the αq subfamily expressed in these cells (91). It may be that the diversity of α and γ subtypes in comparison to the β subunits can provide selectivity in some cases while in other cases the subunits present multiple partners for interaction with the same receptor—the first and most important step in the activation of a signaling pathway. This built-in redundancy could be a mechanism that allows a signaling pathway to continue functioning in the presence of a defective subunit type.

Note added in proof. The identification of a novel γ subunit gene (Huang, L., *et al.* (1999) *Nat. Neurosci.* **2,** 1055–1062; and AL031033) increases the number of known members of this mammalian gene family to 12.

REFERENCES

1. Ahmad, W., Li, S., Chen, H., Tuck-Muller, C. M., Pittler, S. J., and Aronson, N. N. (1995). Lysosomal chitobiase (CTB) and the G-protein γ5 subunit (GNG5) genes co-localize to human chromosome 1p22. *Cytogenet. Cell. Genet.* **71:** 44–46.
2. Asano, T., Morishita, R., Ohashi, K., Nagahama, M., Miyake, T., and Kato, K. (1995). Localization of various forms of the γ subunit of G protein in neural and nonneural tissues. *J. Neurochem.* **64:** 1267–1273.
3. Asano, T., Semba, R., Kamiya, N., Ogasawara, N., and Kato, K. (1988). Go, a GTP-binding protein: Immunochemical and immunohistochemical localization in the rat. *J. Neurochem.* **50:** 1164–1169.
4. Bargmann, C. I. (1998). Neurobiology of the *Caenorhabditis elegans* genome. *Science* **282:** 2028–2033.
5. Belluscio, L., Gold, G. H., Nemes, A., and Axel, R. (1998). Mice deficient in G(olf) are anosmic. *Neuron* **20:** 69–81.
6. Betty, M., Harnish, S. W., Rhodes, K. J., and Cockett, M. I. (1998). Distribution of heterotrimeric G-protein β and γ subunits in the rat brain. *Neuroscience* **85:** 475–486.
7. Brand, E., Herrmann, S. M., Nicaud, V., Ruidavets, J. B., Evans, A., Arveiler, D., Luc, G., Plouin, P. F., Tiret, L., and Cambien, F. (1999). The 825C/T polymorphism of the G-protein subunit β3 is not related to hypertension. *Hypertension* **33:** 1175–1178.
8. Brann, M. R., Collins, R. M., and Spiegel, A. (1987). Localization of mRNAs encoding the α-subunits of signal-transducing G-proteins within rat brain and among peripheral tissues. *FEBS Lett.* **222:** 191–198.
9. Buck, E., Li, J., Chen, Y., Weng, G., Scarlata, S., and Iyengar, R. (1999). Resolution of a signal transfer region from a general binding domain in Gβ for stimulation of phospholipase C-beta2. *Science* **283:** 1332–1335.
10. Cali, J. J., Balcueva, E. A., Rybalkin, I., and Robishaw, J. D. (1992). Selective tissue distribution of G protein gamma subunits, including a new form of the γ subunits identified by cDNA cloning. *J. Biol. Chem.* **267:** 24023–24027.
11. Carter, A., Bardin, C., Collins, R., Simons, C., Bray, P., and Spiegel, A. (1987). Reduced expression of multiple forms of the α subunit of the stimulatory GTP-binding protein in pseudohypoparathyroidism type Ia. *Proc. Natl. Acad. Sci. USA* **84:** 7266–7269.
12. Cerione, R. A., Staniszewski, C., Benovic, J. L., Lefkowitz, R. J., Caron, M. G., Gierschik, P., Somers, R., Spiegel, A. M., Codina, J., and Birnbaumer, L. (1985). Specificity of the functional interactions of the β-adrenergic receptor and rhodopsin with guanine nucleotide regulatory proteins reconstituted in phospholipid vesicles. *J. Biol. Chem.* **260:** 1493–1500.
13. Chen, Y., Weng, G., Li, J., Harry, A., Pieroni, J., Dingus, J., Hildebrandt, J. D., Guarnieri, F., Weinstein, H., and Iyengar, R. (1997). A surface on the G protein β-subunit involved in interactions with adenylyl cyclases. *Proc. Natl. Acad. Sci. USA* **94:** 2711–2714.
14. Clapham, D. E., and Neer, E. J. (1997). G protein $\beta\gamma$ subunits. *Annu. Rev. Pharmacol. Toxicol.* **37:** 167–203.
15. Conklin, B. R., Farfel, Z., Lustig, K. D., Julius, D., and Bourne, H. R. (1993). Substitution of three amino acids switches receptor specificity of Gq alpha to that of Gi α. *Nature* **363:** 274–276.
16. Davies, S. J., and Hughes, H. E. (1993). Imprinting in Albright's hereditary osteodystrophy. *J. Med. Genet.* **30:** 101–103.
17. Davignon, I., Barnard, M., Gavrilova, O., Sweet, K., and Wilkie, T. M. (1996). Gene structure of murine Gna11 and Gna15: Tandemly duplicated Gq class G protein alpha subunit genes. *Genomics* **31:** 359–366.
18. Downes, G. B., Copeland, N. G., Jenkins, N. A., and Gautam, N. (1998). Structure and mapping of the G protein γ3 subunit gene and a divergently transcribed novel gene, Gng31g. *Genomics* **53:** 220–230.
19. Downes, G. B., Gilbert, D. J., Copeland, N. G., Gautam, N., and Jenkins, N. A. (1999). Chromosomal mapping of five mouse G protein γ subunits. *Genomics* **57:** 173–176.
20. Dryja, T. P., Hahn, L. B., Reboul, T., and Arnaud, B. (1996). Missense mutation in the gene encoding the α subunit of rod transducin in the Nougaret form of congenital stationary night blindness. *Nat. Genet.* **13:** 358–360.
21. Farfel, Z., Bourne, H. R., and Iiri, T. (1999). The expanding spectrum of G protein diseases. *N. Engl. J. Med.* **340:** 1012–1020.

22. Fisher, K. J., and Aronson, N. N., Jr. (1992). Characterization of the cDNA and genomic sequence of a G protein γ subunit (γ5). *Mol. Cell. Biol.* **12:** 1585–1591.
23. Fong, H. K., Amatruda, T. T. D., Birren, B. W., and Simon, M. I. (1987). Distinct forms of the β subunit of GTP-binding regulatory proteins identified by molecular cloning. *Proc. Natl. Acad. Sci. USA* **84:** 3792–3796.
24. Fong, H. K., Yoshimoto, K. K., Eversole-Cire, P., and Simon, M. I. (1988). Identification of a GTP-binding protein α subunit that lacks an apparent ADP-ribosylation site for pertussis toxin. *Proc. Natl. Acad. Sci. USA* **85:** 3066–3070.
25. Ford, C. E., Skiba, N. P., Bae, H., Daaka, Y., Reuveny, E., Shekter, L. R., Rosal, R., Weng, G., Yang, C. S., Iyengar, R., Miller, R. J., Jan, L. Y., Lefkowitz, R. J., and Hamm, H. E. (1998). Molecular basis for interactions of G protein βγ subunits with effectors. *Science* **280:** 1271–1274.
26. Gautam, N., Baetscher, M., Aebersold, R., and Simon, M. I. (1989). A G protein γ subunit shares homology with ras proteins. *Science* **244:** 971–974.
27. Gautam, N., Downes, G. B., Yan, K., and Kisselev, O. (1998). The G protein βγ complex. *Cell. Signalling* **10:** 447–455.
28. Gautam, N., Northup, J., Tamir, H., and Simon, M. I. (1990). G protein diversity is increased by associations with a variety of γ subunits. *Proc. Natl. Acad. Sci. USA* **87:** 7973–7977.
29. Gilman, A. G. (1987). G proteins: Transducers of receptor-generated signals. *Annu. Rev. Biochem.* **56:** 615–649.
30. Glockner, G., Scherer, S., Schattevoy, R., Boright, A., Weber, J., Tsui, L. C., and Rosenthal, A. (1998). Large-scale sequencing of two regions in human chromosome 7q22: Analysis of 650 kb of genomic sequence around the EPO and CUTL1 loci reveals 17 genes. *Genome Res.* **8:** 1060–1073.
31. Gudermann, T., Schoneberg, T., and Schultz, G. (1997). Functional and structural complexity of signal transduction via G-protein-coupled receptors. *Annu. Rev. Neurosci.* **20:** 399–427.
32. Hamm, H. E. (1998). The many faces of G protein signaling. *J. Biol. Chem.* **273:** 669–672.
33. Hamm, H. E., Deretic, D., Arendt, A., Hargrave, P. A., Koenig, B., and Hofmann, K. P. (1988). Site of G protein binding to rhodopsin mapped with synthetic peptides from the α subunit. *Science* **241:** 832–835.
34. Itoh, H., Toyama, R., Kozasa, T., Tsukamoto, T., Matsuoka, M., and Kaziro, Y. (1988). Presence of three distinct molecular species of Gi protein α subunit. Structure of rat cDNAs and human genomic DNAs. *J. Biol. Chem.* **263:** 6656–6664.
35. Jansen, G., Thijssen, K. L., Werner, P., van der Horst, M., Hazendonk, E., and Plasterk, R. H. (1999). The complete family of genes encoding G proteins of *Caenorhabditis elegans*. *Nat. Genet.* **21:** 414–419.
36. Jiang, M., Gold, M. S., Boulay, G., Spicher, K., Peyton, M., Brabet, P., Srinivasan, Y., Rudolph, U., Ellison, G., and Birnbaumer, L. (1998). Multiple neurological abnormalities in mice deficient in the G protein Go. *Proc. Natl. Acad. Sci. USA* **95:** 3269–3274.
37. Jones, D. T., and Reed, R. R. (1987). Molecular cloning of five GTP-binding protein cDNA species from rat olfactory neuroepithelium. *J. Biol. Chem.* **262:** 14241–14249.
38. Kalyanaraman, S., Copeland, N. G., Gilbert, D. J., Jenkins, N. A., and Gautam, N. (1998). Structure and chromosomal localization of mouse G protein subunit γ4 gene. *Genomics* **49:** 147–151.
39. Kalyanaraman, S., Kalyanaraman, V., and Gautam, N. (1995). A brain-specific G protein γ subunit. *Biochem. Biophys. Res. Commun.* **216:** 126–132.
40. Kato, N., Sugiyama, T., Morita, H., Kurihara, H., Yamori, Y., and Yazaki, Y. (1998). G protein β3 subunit variant and essential hypertension in Japanese. *Hypertension* **32:** 935–938.
41. Kaziro, Y., Itoh, H., Kozasa, T., Nakafuku, M., and Satoh, T. (1991). Structure and function of signal-transducing GTP-binding proteins. *Annu. Rev. Biochem.* **60:** 349–400.
42. Kehlenbach, R. H., Matthey, J., and Huttner, W. B. (1994). XL αs is a new type of G protein. *Nature* **372:** 804–809. [Published erratum appears in *Nature*, 1995 May 18;**375**(6528):253]
43. Kisselev, O., and Gautam, N. (1993). Specific interaction with rhodopsin is dependent on the γ subunit type in a G protein. *J. Biol. Chem.* **268:** 24519–24522.
44. Kisselev, O., Pronin, A., Ermolaeva, M., and Gautam, N. (1995). Receptor-G protein coupling is established by a potential conformational switch in the βγ complex. *Proc. Natl. Acad. Sci. USA* **92:** 9102–9106.
45. Kleuss, C., Hescheler, J., Ewel, C., Rosenthal, W., Schultz, G., and Wittig, B. (1991). Assignment of G-protein subtypes to specific receptors inducing inhibition of calcium currents. *Nature* **353:** 43–48.
46. Kozasa, T., Itoh, H., Tsukamoto, T., and Kaziro, Y. (1988). Isolation and characterization of the human Gs α gene. *Proc. Natl. Acad. Sci. USA* **85:** 2081–2085.
47. Lambright, D. G., Sondek, J., Bohm, A., Skiba, N. P., Hamm, H. E., and Sigler, P. B. (1996). The 2.0 A crystal structure of a heterotrimeric G protein. *Nature* **379:** 311–319.
48. Largent, B. L., Jones, D. T., Reed, R. R., Pearson, R. C., and Snyder, S. H. (1988). G protein mRNA mapped in rat brain by in situ hybridization. *Proc. Natl. Acad. Sci. USA* **85:** 2864–2868.
49. Lerea, C. L., Somers, D. E., Hurley, J. B., Klock, I. B., and Bunt-Milam, A. H. (1986). Identification of specific transducin α subunits in retinal rod and cone photoreceptors. *Science* **234:** 77–80.
50. Levay, K., Cabrera, J. L., Satpaev, D. K., and Slepak, V. Z. (1999). Gbeta5 prevents the RGS7-Galphao interaction through binding to a distinct Gγ-like domain found in RGS7 and other RGS proteins. *Proc. Natl. Acad. Sci. USA* **96:** 2503–2507.
51. Levine, M. A., Ahn, T. G., Klupt, S. F., Kaufman, K. D., Smallwood, P. M., Bourne, H. R., Sullivan, K. A., and Van Dop, C. (1988). Genetic deficiency of the alpha subunit of the guanine nucleotide-binding protein Gs as the molecular basis for Albright hereditary osteodystrophy. *Proc. Natl. Acad. Sci. USA* **85:** 617–621.
52. Levine, M. A., Smallwood, P. M., Moen, P. T., Jr., Helman, L. J., and Ahn, T. G. (1990). Molecular cloning of β3 subunit, a third form of the G protein beta-subunit polypeptide. *Proc. Natl. Acad. Sci. USA* **87:** 2329–2333.
53. Liang, J. J., Cockett, M., and Khawaja, X. Z. (1998). Immunohistochemical localization of G protein β1, β2, β3, β4, β5, and γ3 subunits in the adult rat brain. *J. Neurochem.* **71:** 345–355.
54. Lindorfer, M. A., Myung, C. S., Savino, Y., Yasuda, H., Khazan, R., and Garrison, J. C. (1998). Differential activity of the G protein β5 γ2 subunit at receptors and effectors. *J. Biol. Chem.* **273:** 34429–34436.
55. Liu, B., and Aronson, N. N., Jr. (1998). Structure of human G protein Gγ5 gene GNG5. *Biochem. Biophys. Res. Commun.* **251:** 88–94.
56. Matsuoka, M., Itoh, H., and Kaziro, Y. (1990). Characterization of the human gene for Gx α a pertussis toxin-insensitive regulatory GTP-binding protein. *J. Biol. Chem.* **265:** 13215–13220.
57. McLaughlin, S. K., McKinnon, P. J., and Margolskee, R. F. (1992). Gustducin is a taste-cell-specific G protein closely related to the transducins. *Nature* **357:** 563–569.
58. Morishita, R. N. H., Isobe, T., Matsuda, T., Hashimoto, Y., Okano, T., Fukada, Y., Mizuno, K., Ohno, S., Kozawa, O., Kato, K., and Asano, T. (1995). Primary structure of a γ subunit of G protein G12, and its phosphorylation by protein kinase C. *J. Biol. Chem.* **270:** 29469–29475.
59. Moss, J., and Vaughan, M. (1988). ADP-ribosylation of guanyl nucleotide-binding regulatory proteins by bacterial toxins. *Adv. Enzymol. Relat. Areas Mol. Biol.* **61:** 303–379.

60. Neer, E. J. (1995). Heterotrimeric G proteins: Organizers of transmembrane signals. *Cell* **80:** 249–257.
61. Offermanns, S., Mancino, V., Revel, J. P., and Simon, M. I. (1997). Vascular system defects and impaired cell chemokinesis as a result of Gα13 deficiency. *Science* **275:** 533–536.
62. Offermanns, S., and Simon, M. I. (1998). Genetic analysis of mammalian G-protein signalling. *Oncogene* **17:** 1375–1381.
63. Offermanns, S., Toombs, C. F., Hu, Y. H., and Simon, M. I. (1997). Defective platelet activation in Gα(q)-deficient mice. *Nature* **389:** 183–186.
64. Ong, O. C., Hu, K., Rong, H., Lee, R. H., and Fung, B. K. (1997). Gene structure and chromosome localization of the Gγc subunit of human cone G-protein (GNGT2). *Genomics* **44:** 101–109.
65. Peng, Y. W., Robishaw, J. D., Levine, M. A., and Yau, K. W. (1992). Retinal rods and cones have distinct G protein β and γ subunits. *Proc. Natl. Acad. Sci. USA* **89:** 10882–10886.
66. Peters, J., Wroe, S. F., Wells, C. A., Miller, H. J., Bodle, D., Beechey, C. V., Williamson, C. M., and Kelsey, G. (1999). A cluster of oppositely imprinted transcripts at the Gnas locus in the distal imprinting region of mouse chromosome 2. *Proc. Natl. Acad. Sci. USA* **96:** 3830–3835.
67. Raport, C. J., Dere, B., and Hurley, J. B. (1989). Characterization of the mouse rod transducin α subunit gene. *J. Biol. Chem.* **264:** 7122–7128.
68. Ray, K., Kunsch, C., Bonner, L. M., and Robishaw, J. D. (1995). Isolation of cDNA clones encoding eight different human G protein γ subunits, including three novel forms designated the γ4, γ10, and γ11 subunits. *J. Biol. Chem.* **270:** 21765–21771.
69. Richardson, M., and Robishaw, J. D. (1999). The α2A-adrenergic receptor discriminates between Gi heterotrimers of different βγ subunit composition in Sf9 insect cell membranes. *J. Biol. Chem.* **274:** 13525–13533.
70. Rubio, J. P., Levy, E. R., Dobson-Stone, C., and Monaco, A. P. (1999). Genomic organization of the human Gα14 and Gαq genes and mutation analysis in chorea-acanthocytosis (CHAC). *Genomics* **57:** 84–93.
71. Ryba, N. J., and Tirindelli, R. (1995). A novel GTP-binding protein γ-subunit, G gamma 8, is expressed during neurogenesis in the olfactory and vomeronasal neuroepithelia. *J. Biol. Chem.* **270:** 6757–6767.
72. Scherer, S. W., Feinstein, D. S., Oliveira, L., Tsui, L. C., and Pittler, S. J. (1996). Gene structure and chromosome localization to 7q21.3 of the human rod photoreceptor transducin γ-subunit gene (GNGT1). *Genomics* **35:** 241–243.
73. Siffert, W., Rosskopf, D., Siffert, G., Busch, S., Moritz, A., Erbel, R., Sharma, A. M., Ritz, E., Wichmann, H. E., Jakobs, K. H., and Horsthemke, B. (1998). Association of a human G-protein β3 subunit variant with hypertension. *Nat. Genet.* **18:** 45–48. [See comments]
74. Simon, M. I., Strathmann, M. P., and Gautam, N. (1991). Diversity of G proteins in signal transduction. *Science* **252:** 802–808.
75. Sondek, J., Bohm, A., Lambright, D. G., Hamm, H. E., and Sigler, P. B. (1996). Crystal structure of a G-protein βγ dimer at 2.1 Å resolution. *Nature* **379:** 369–374. [Published erratum appears in *Nature* 1996 Feb 29; **379**(6568): 847]
76. Spiegel, A. M. (1996). Defects in G protein-coupled signal transduction in human disease. *Annu. Rev. Physiol.* **58:** 143–170.
77. Strathmann, M. P., and Simon, M. I. (1991). Gα12 and Gα13 subunits define a fourth class of G protein α subunits. *Proc. Natl. Acad. Sci. USA* **88:** 5582–5586.
78. Strathmann, M., Wilkie, T. M., and Simon, M. I. (1990). Alternative splicing produces transcripts encoding two forms of the α subunit of GTP-binding protein Go. *Proc. Natl. Acad. Sci. USA* **87:** 6477–6481.
79. Sullivan, K. A., Liao, Y. C., Alborzi, A., Beiderman, B., Chang, F. H., Masters, S. B., Levinson, A. D., and Bourne, H. R. (1986). Inhibitory and stimulatory G proteins of adenylate cyclase: cDNA and amino acid sequences of the α chains. *Proc. Natl. Acad. Sci. USA* **83:** 6687–6691.
80. Tao, L., Pandey, S., Simon, M. I., and Fong, H. K. (1993). Structure of the bovine transducin γ subunit gene and analysis of promoter function in transgenic mice. *Exp. Eye Res.* **56:** 497–507.
81. Tsukamoto, T., Toyama, R., Itoh, H., Kozasa, T., Matsuoka, M., and Kaziro, Y. (1991). Structure of the human gene and two rat cDNAs encoding the alpha chain of GTP-binding regulatory protein Go: Two different mRNAs are generated by alternative splicing. *Proc. Natl. Acad. Sci. USA* **88:** 2974–2978.
82. Valenzuela, D., Han, X., Mende, U., Fankhauser, C., Mashimo, H., Huang, P., Pfeffer, J., Neer, E. J., and Fishman, M. C. (1997). Gα(o) is necessary for muscarinic regulation of Ca^{2+} channels in mouse heart. *Proc. Natl. Acad. Sci. USA* **94:** 1727–1732.
83. von Weizsacker, E., Strathmann, M. P., and Simon, M. I. (1992). Diversity among the β subunits of heterotrimeric GTP-binding proteins: Characterization of a novel β-subunit cDNA. *Biochem. Biophys. Res. Commun.* **183:** 350–356.
84. Wall, M. A., Coleman, D. E., Lee, E., Iniguez-Lluhi, J. A., Posner, B. A., Gilman, A. G., and Sprang, S. R. (1995). The structure of the G protein heterotrimer Gi α1 β1 gamma 2. *Cell* **83:** 1047–1058.
85. Watson, A. J., Aragay, A. M., Slepak, V. Z., and Simon, M. I. (1996). A novel form of the G protein β subunit Gbeta5 is specifically expressed in the vertebrate retina. *J. Biol. Chem.* **271:** 28154–28160.
86. Watson, A. J., Katz, A., and Simon, M. I. (1994). A fifth member of the mammalian G-protein beta-subunit family. Expression in brain and activation of the β2 isotype of phospholipase C. *J. Biol. Chem.* **269:** 22150–22156.
87. Watson, J. B., Coulter, P. M. N., Margulies, J. E., de Lecea, L., Danielson, P. E., Erlander, M. G., and Sutcliffe, J. G. (1994). G-protein γ 7 subunit is selectively expressed in medium-sized neurons and dendrites of the rat neostriatum. *J. Neurosci. Res.* **39:** 108–116.
88. Weinstein, L. S., Shenker, A., Gejman, P. V., Merino, M. J., Friedman, E., and Spiegel, A. M. (1991). Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *N. Engl. J. Med.* **325:** 1688–1695.
89. Wilkie, T. M., Gilbert, D. J., Olsen, A. S., Chen, X. N., Amatruda, T. T., Korenberg, J. R., Trask, B. J., de Jong, P., Reed, R. R., Simon, M. I., *et al.* (1992). Evolution of the mammalian G protein α subunit multigene family. *Nat. Genet.* **1:** 85–91.
90. Wilkie, T. M., Scherle, P. A., Strathmann, M. P., Slepak, V. Z., and Simon, M. I. (1991). Characterization of G-protein α subunits in the Gq class: Expression in murine tissues and in stromal and hematopoietic cell lines. *Proc. Natl. Acad. Sci. USA* **88:** 10049–10053.
91. Xu, X., Croy, J. T., Zeng, W., Zhao, L., Davignon, I., Popov, S., Yu, K., Jiang, H., Offermanns, S., Muallem, S., and Wilkie, T. M. (1998). Promiscuous coupling of receptors to Gq class α subunits and effector proteins in pancreatic and submandibular gland cells. *J. Biol. Chem.* **273:** 27275–27279.
92. Yan, K., and Gautam, N. (1996). A domain on the G protein β subunit interacts with both adenylyl cyclase 2 and the muscarinic atrial potassium channel. *J. Biol. Chem.* **271:** 17597–17600.
93. Yan, K., and Gautam, N. (1997). Structural determinants for interaction with three different effectors on the G protein β subunit. *J. Biol. Chem.* **272:** 2056–2059.
94. Yu, S., Yu, D., Lee, E., Eckhaus, M., Lee, R., Corria, Z., Accili, D., Westphal, H., and Weinstein, L. S. (1998). Variable and tissue-specific hormone resistance in heterotrimeric Gs protein α-subunit (Gsα) knockout mice is due to tissue-specific imprinting of the gsα gene. *Proc. Natl. Acad. Sci. USA* **95:** 8715–8720.
95. Zhang, S., Coso, O. A., Lee, C., Gutkind, J. S., and Simonds, W. F. (1996). Selective activation of effector pathways by brain-specific G protein β5. *J. Biol. Chem.* **271:** 33575–33579.